CLINICAL OUTCOMES OF RENAL TRANSPLANTATION IN HEPATITIS C VIRUS POSITIVE RECIPIENTS

Dissertation submitted to

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BRANCH – III,

DEPARTMENT OF NEPHROLOGY,

MADRAS MEDICAL COLLEGE,

CHENNAI – 600 003.

THE TAMIL NADU

DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI

AUGUST 2014

CERTIFICATE

This is to certify that this Dissertation entitled **CLINICAL OUTCOMES OF RENAL TRANSPLANTATION IN HEPATITIS C VIRUS POSITIVE RECIPIENTS** is a bonafide work done by **Dr.S.SUJIT,** Madras Medical College, Chennai-03 in partial fulfilment of the University rules and regulations for award of D.M. (Nephrology) under my guidance and supervision during the academic year August 2014.

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DECLARATION

I, **Dr. S. SUJIT,** solemnly declare that the dissertation titled **CLINICAL OUTCOMES OF RENAL TRANSPLANTATION IN HEPATITIS C VIRUS POSITIVE RECIPIENTS** is the bonafide work done by me at Department of Nephrology, Madras Medical College under the expert guidance and supervision of **Dr.N.GOPALAKRISHNAN, D.M, FRCP,** Professor of Nephrology, Madras Medical College. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards partial fulfilment of requirement for the award of D.M. Degree (Branch III) in Nephrology.

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Above all I thank the Lord Almighty for His kindness and benevolence.

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INTRODUCTION

Hepatitis C virus(HCV) infects 20-50% of chronic kidney disease patients(47).The number of chronic kidney disease patients is on increasing trend . The number of chronic kidney disease patients undergoing dialysis is also increasing. Various studies have shown that 3.4-43% of chronic kidney disease patients undergoing maintenance hemodialysis test positive for anti HCV antibodies (48).

Hepatitis C virus infection confers 1.62-2.39 fold increase in risk of death for hemodialysis patients (49).

Various studies have shown that quality of life, morbidity and mortality of chronic kidney disease patients on maintenance hemodialysis is worse when compared to the quality of life, morbidity and mortality of patients undergoing renal transplantation. For these reasons, renal transplantation is better therapeutic option for hepatitis C virus infected patients on maintenance hemodialysis. Anti viral therapy for hepatitis C virus should be given before transplantation. The recommendation is to screen for hepatitis C virus infected patients on transplant programme by testing antibodies for hepatitis C virus

If antibodies to hepatitis C virus is detected , we should proceed testing hepatitis C virus RNA . If hepatitis C Virus RNA is detected , genotyping should be done. Based on the genotype , interferon should be given before

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INSTITUTIONAL ETHICS COMMITTEE
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CERTIFICATE OF APPROVAL

To
Dr. Sujit.S
PG in DM Nephrology
Madras Medical College, Chennai -3

Dear Dr. Sujit.S

The Institutional Ethics Committee of Madras Medical College reviewed and discussed your application for approval of the proposal entitled "Clinical outcomes of renal transplatiation in hepatitis c virus positive recipients " No. 30052012.

The following members of Ethics Committee were present in the meeting held on 30.05.2012 conducted at Madras Medical College, Chennai -3.

1.	Prof. S.K. Rajan, MD	-- Chairperson
2.	Prof. Pregna B. Dolia MD Vice Principal , Madras Medical College, Chennai -3 Director , Instt.of Bio Chemistry, MMC, Ch-3	-- Member Secretary
3.	Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
4.	Prof. P. Karkuzhali MD Director i/c Prof & Head , Dept. of Pathology, MMC, Ch-3	-- Member
5.	Prof.A. Radhakrishnan MD Prof. of Internal Medicine, MMC, Ch-3	-- Member
6.	Prof. P. Raghumani MS Prof. of Surgery, Dept. of Surgery, MMC, Chennai -3	-- Member
7.	Thiru. S. Govindasamy . BA.BL	-- Lawyer
8.	Tmt. Arnold Soulina MA	-- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

CONTENTS

INTRODUCTION

Hepatitis C virus(HCV) infects 20-50% of chronic kidney disease patients[47]. The number of chronic kidney disease patients is on increasing trend . The number of chronic kidney disease patients undergoing dialysis is also increasing. Various studies have shown that 3.4-43% of chronic kidney disease patients undergoing maintenance hemodialysis test positive for anti HCV antibodies [48].

Hepatitis C virus infection confers 1.62-2.39 fold increase in risk of death for hemodialysis patients [49].

Various studies have shown that quality of life, morbidity and mortality of chronic kidney disease patients on maintenance hemodialysis is worse when compared to the quality of life, morbidity and mortality of patients undergoing renal transplantation. For these reasons, renal transplantation is better therapeutic option for hepatitis C virus infected patients on maintenance hemodialysis. Anti viral therapy for hepatitis C virus should be given before transplantation. The recommendation is to screen for hepatitis C virus infected patients on transplant programme by testing antibodies for hepatitis C virus.

If antibodies to hepatitis C virus is detected, we should proceed testing hepatitis C virus RNA . If hepatitis C Virus RNA is detected, genotyping should be done. Based on the genotype , interferon should be given before transplant. Patients attaining sustained viral response after interferon therapy should be taken for renal transplant, after ruling out clinical and biochemical evidence of liver cirrhosis.

Most of the available studies has shown that the patient and graft survival is worse in hepatitis C virus infected recipients when compared with hepatitis C uninfected recipients. The incidence of acute rejection , new onset of diabetes mellitus after transplant(NODAT),sepsis, interstitial fibrosis and tubular atrophy , progression of liver disease is higher in hepatitis C virus infected recipients when compared with hepatitis C uninfected recipients. Hepatitis C virus infected recipients are also at risk of developing glomerular diseases like membrano proliferative glomerulonephritis with or without cryoglobulinemia , membranous glomerulonephritis, thrombotic microangiopathy.

After transplant, interferon given increases the immunogenicity of the graft leading to graft loss. The only indications for giving interferon post transplant are fibrosing cholestasis and life threatening vasculitis.

AIMS AND OBJECTIVES

AIM OF THE STUDY

To study of clinical outcomes of renal transplantation in hepatitis C virus positive renal transplantation recipients.

PRIMARY OBJECTIVES

To assessing the all cause mortality among hepatitis c virus positive recipients.

SECONDARY OBJECTIVE

1. Graft dysfunction
2. Acute rejection
3. New onset of diabetes mellitus
4. Sepsis and associated infections.
5. Proteinuria
6. Interstitial fibrosis and tubular atrophy.
7. Liver cell failure.

METHODOLOGY

STUDY POPULATION

Patients on live related and cadaver transplantation programme were screened for Hepatitis C virus by anti HCV antibody testing and qualitative HCV RNA load, patients who were found to be positive for hepatitis c virus and underwent either live related or cadaver transplantation in our department during 2010 -2013 were followed in our ward and out patient department.

INCLUSION CRITERIA

Patients who were found to have hepatitis C virus positive patients who underwent either live related or cadaver transplantation in our department.

EXCLUSION CRITERIA

Pre transplant liver cirrhosis

Pre transplant diabetes mellitus

Hepatitis B virus positive renal failure patients.

STUDY DESIGN

Single Arm Retrospective and Prospective Observational study.

SUBJECTS AND METHODS

Patients who were eligible for either live related or cadaver renal transplant during their pre transplant work up were screened for diabetes mellitus by blood sugar testing; liver cirrhosis by liver function test, ultrasound, portal doppler, upper gastro intestinal endoscopy; hepatitis c virus by anti h c v antibody testing and qualitative hepatitis C RNA viral load, Hepatitis B virus by HBsAg.

Patients who were found to have hepatitis c virus positive and not having diabetes mellitus, clinical liver cirrhosis undergoing either live related or cadaver renal transplantation were included in my study.

DEFINITIONS USED

SUSTAINED VIRAL RESPONSE:

After treatment with interferon RNA levels should be < 50 iu /ml for six months.

DELAYED GRAFT FUNCTION:

Requirement of hemodialysis within seven days of transplantation.

POST TRANSPLANT LIVER DYSFUNCTION:

Depending on the degree of elevation of liver enzymes (aspartate aminotransferae and alanine aminotransferase)

MILD CHRONIC LIVER DYSFUNCTION(> 6 MONTHS)

Rise in liver enzymes upto two and half times the normal levels.

MODERATE CHRONIC LIVER DYSFUNCTION (>6MONTHS)

Elevation in liver enzymes more than two and half times the normal levels.

ACUTE HEPATITIS (> 7 DAYS <6MONTHS)

Elevation in liver enzymes more than two and half times of normal .

DECOMPENSATED CHRONIC LIVER DISEASE :

Occurrence of one clinical jaundice, fluid in the abdomen, encephalopathy due to liver pathology, bleeding from the varices in the gastro intestinal tract .

NEW ONSET OF DIABETES MELLITUS AFTER TRANSPLANT (NODAT):

Patients with no history of diabetes mellitus or treatment for diabetes mellitus undergoing transplantation and developing diabetes mellitus after transplant requiring treatment.

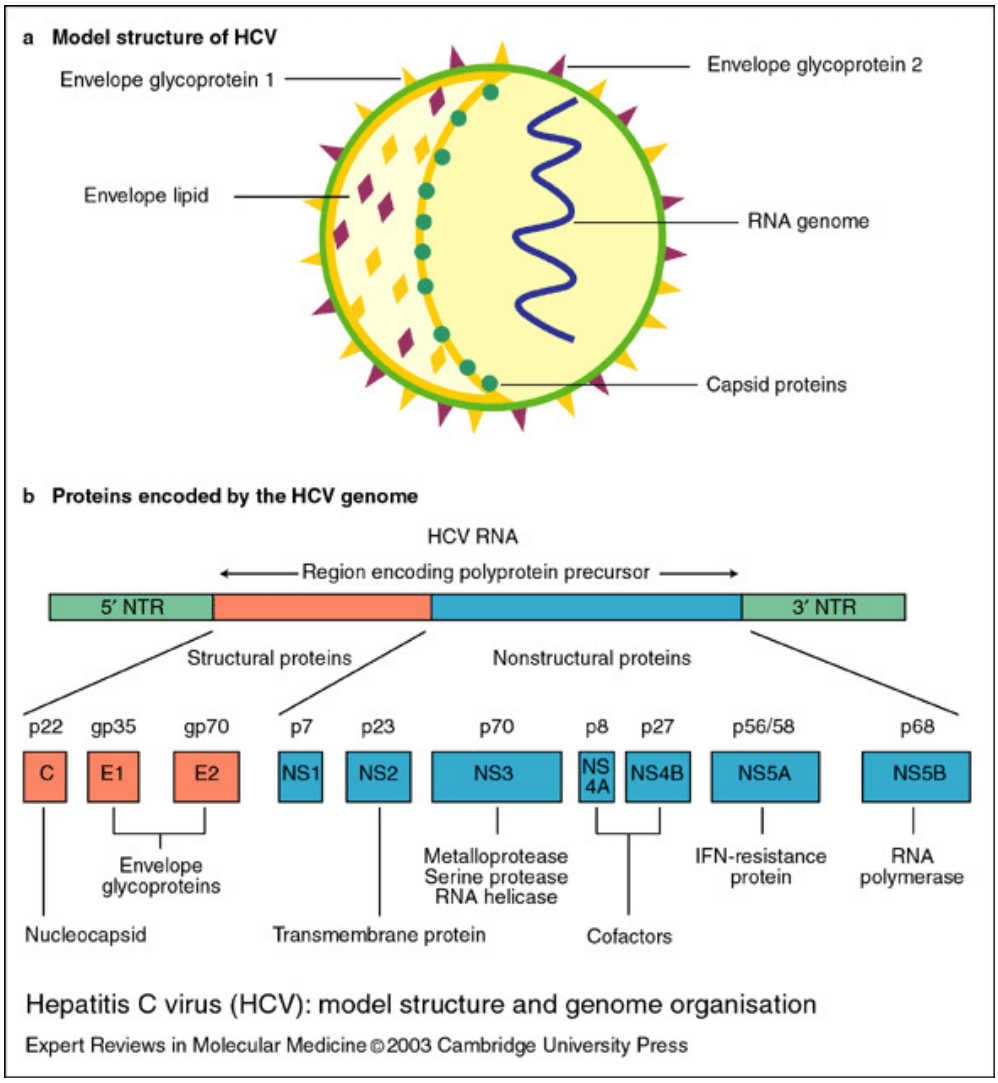
STATISTICAL ANALYSIS

Data analysed with SPSS software version 16.0 for windows. All continuous data expressed as mean +/- standard deviation . Continuous data analysed using unpaired t test. Categorical data expressed as number (percentage) . Fishers exact test were used to analyze the categorical data. A p value of <0.05 is significant statistically.

Univariate analysis done to evaluate odds ratio with confidence interval and relative risk of various parameters that increases the risk of HCV infection among recipients.

REVIEW OF LITERATURE

Hepatitis C virus (HCV) is a RNA virus. This virus belongs to flaviviridae family. The RNA genome of HCV is single stranded and positive stranded. Its length is 9.6 kb with a single open reading frame. It encodes a single polyprotein precursor of approximately 3000 residues which are flanked on both sides by untranslated regions [1].



Hepatitis C virus (HCV): model structure and genome organisation

Expert Reviews in Molecular Medicine ©2003 Cambridge University Press

Ten different proteins are produced upon cleavage of precursor polyprotein. It includes 4 structural proteins which includes core protein, envelope protein (E1), envelope protein 2(E2), small polypeptide protein(p7) and 6 non structural protein-non structural protein (NS2,NS3,NS4A,NS4B, NS5A and NS5B).

Genetic variability is a characteristic feature of HCV genome, it is of high degree. Mutation rates of various regions in the viral genome is variable. The most variable regions are envelope E1 and E2. The viral genome sequence are highly conserved in the 5' UTR and terminal segment of 3' UTR. The imperfect proof reading of the viral RNA dependent RNA polymerase accounts for this high degree of mutation rate. This causes co existence of different mutants of the parent strain as quasispecies [(2)].

As cell cultures for HCV are not present, studies of infectivity have come from chimpanzee. When chimpanzees are exposed to hepatitis C virus, HCV RNA appears in the serum within 1-2 weeks, followed by elevation of serum alanine amino transferase 3-6 weeks, followed by development of antibodies against HCV core NS3 and NS4.

EPIDEMIOLOGY

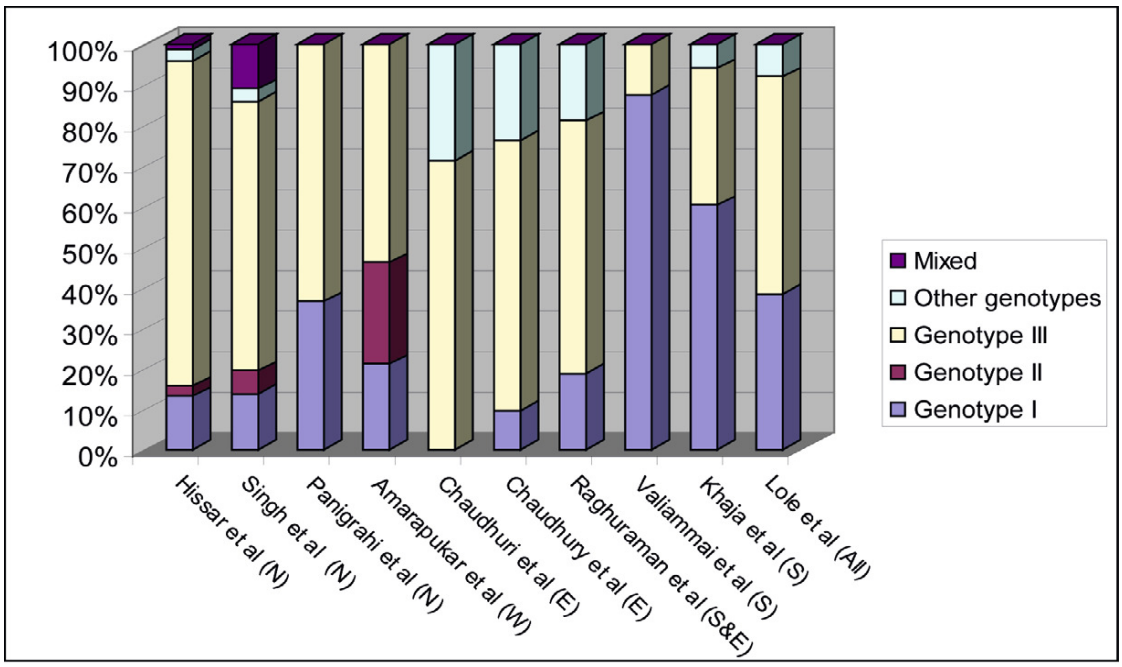
The strains from different geographical regions have large differences in the HCV genome . This leads to classification into six major

genotypes. The commonest genotype throughout the world are type 1,2 and 3. The commonest genotype in north africa and middle east is type 4. The commonest genotype in south Africa is type 5 . The commonest genotype in south east asia is type 6. [3][4]

The classification of HCV into various genotypes is a major predictor of anti viral treatment response. Genotype 1 has a poorer response to treatment with interferon and progression of severe chronic hepatitis. It neither has an impact on clinical presentation of the disease nor the severity of the disease.

In northern, eastern and western india genotype 3 is common .In southern india genotype 1 is common.

Proportion of various genotypes in India



Studies from North india –N; West india –W; East india –E; South and east india –S&E ; South india-S; Throughout india AII [5].

World wide there is varied prevalence of hepatitis c virus infection in chronic kidney disease patients undergoing dialysis, ranging from less than one percent to more than seventy percent.

In chronic kidney disease patients in hemodialysis the prevalence of infection with HCV is 12- 42% in India [6].

HCV infection prevalence can vary between each dialysis unit within a country. The important factors that confers increased for HCV infection include blood transfusions without proper screening for hepatitis c virus, duration of dialysis and change in the number of dialysis centers .

LABORATORY DIAGNOSIS OF H C V

HCV is diagnosed by three following methods :

1. Testing serology for antibodies against hepatitis c virus antigens.
2. Test to detect and quantify hepatitis c virus antigens.
3. Test that detects and quantifies hepatitis c virus genomes .Test that sequences the HCV genome.

Tests that are routinely used to screen and diagnose hepatitis C virus infection are serologic and bio–molecular based .

Serological tests include enzyme immunoassay (EIA), recombinant immunoblot assay (RIBA) and tests to detect specific genotype antibodies.

Molecular tests are,

- Quantitative tests which detects hepatitis C virus RNA,
- Quantitative tests which measures the load of H C V- index for replication of HCV
- Test which sequence the hepatitis c virus genome [7].

HCV RNA DETECTION AND QUANTIFICATION

QUALITATIVE HCV RNA TESTS

These tests uses target amplification principle. Qualitative HCV RNA tests are done either by polymerase chain reaction or by target mediated amplification methods.

QUANTITATIVE HCV RNA TESTS

By using the methods that amplifies the target (polymerase chain reaction either conventional or real time) and methods that amplify the signal (branched DNA) HCV RNA is quantified.

INTERPERATION OF TESTS:

Chronic kidney disease patients on hemodialysis will have a lower transaminase levels when compared to individuals with normal renal function. Normal transaminases levels have been documented in 25% of

patients with HCV infection. HCV infection should be suspected whenever there is elevation of transaminase [8]. After 1-2 weeks of exposure to hepatitis c virus only, HCV RNA is detected.

After 8 weeks of hepatitis c virus exposure, anti HCV antibodies are detected. So, we can't exclude HCV infection by a negative anti HCV test [9].

The detection of hepatitis c virus antibodies by serological tests implies that the patient is having acute or chronic infection, but these tests cannot discriminate acute infection from chronic or resolved infection.

In about 50-93% of the patients with acute hepatitis c virus infection and 50-93% of chronic hepatitis c virus infection , anti hepatitis c virus IgM antibodies cannot be detected, which implies that in diagnosing acute infection these serological tests are not a reliable indicator.

In low risk patients (healthy blood donors) and in high risk patients who are negative for hepatitis c virus RNA, recombinant immunoblot assay (RIBA) is needed. For patients with indeterminate RIBA results , sensitive tests which detect hepatitis C virus RNA should be done.

Qualitative RNA tests should be done in patients with acute hepatitis of uncertain orgin and patients whose tests for serology is negative.

HCV RNA tests are also used in few immunocompromised patients, in hemodialysis patients and in mixed cyroglobulemic patients who test false negative on serology.

HEPATITIS C VIRUS AND KIDNEY

HCV causes various glomerular lesions, especially membrano proliferative glomerular lesions associated with or without cryoglobulinemia, focal segmental glomerulosclerosis and membranous glomerulonephritis. In diabetic chronic kidney disease patients, HCV infection causes the glomerular filtration rate tom decline rapidly [10].

Chronic kidney disease patients on hemodialysis, have higher prevalence of infection of hepatitis C virus when compared to general population. These patients are also associated with increased mortality rate[11].

PREVALANCE OF HCV INFECTION IN CKD

Worldwide the prevalence of HCV infection in chronic hemo dialysis, ranging from less than one percent to more than seventy percent.

According to the study by Saha D and SK Agarwal in India the HCV prevalence was 12-42% in 2001[12].

The prevalence of hepatitis C virus can vary between each dialysis unit within a country.

The notable factors that increases the risk for hepatitis C virus infection are blood transfusion without proper screening for HCV ,use of intravenous drugs , duration of dialysis ,number of dialysis centers patient underwent dialysis, patient undergoing dialysis in a dialysis center with high prevalence of Hepatitis C virus, history of renal transplantation.

TRANSPLANTATION IS A BETTER OPTION THAN DIALYSIS

When comparing the dialysis patients infected with hepatitis C virus , renal transplantation is a better outcome. The evidence for this better outcome comes from three studies.

The study by BRAIN J.G. PEREIRA et al, states the beneficial rather than adverse effect of renal transplantation on long term survival in anti HCV positive patients when compared to HCV infected patients on dialysis[13].

Study by KNOLL et al, concludes that the survival of HCV infected patients on dialysis is decreased when compared to hepatitis C virus infected renal transplanted recipients.[14].

Study by BLOOM et al, retrospectively compared 138 renal transplant HCV virus positive recipients with 177 HCV positive dialysis

patients, renal transplant wait listed patients. The mortality of transplanted recipients was approximately 20 % and mortality of hepatitis c virus positive patients was approximately 50%, with p =0.003[15].

TREATMENT FOR HEPATITIS C VIRUS

INTERFERON ALFA

This parenteral drug acts by binding to specific membrane receptors on cell surface. It acts by suppressing the proliferation of virus infected cells, modulating the immune activity of host cells, inhibition of replication of virus.

PEG INTERFERON ALFA

These agents have polyethyelene glycol moiety attached by a covalent bond. This modification prolongs the terminal half life and slows the clearance .

RIBAVIRIN

This anti viral agent is a gaunosine analog, enzymes present in the host phosphorylates intracellularly.

It exerts it anti viral property by interfering the synthesis of guanosine triphosphate, causes inhibition of viral m RNA capping. It also inhibits RNA dependent RNA polymerase.

TELAPREVIR , BOCEPREVIR

These drugs act by inhibiting non structural protease NS 3/ NS 4A

MIRAVIRSEN

Inhibits microRNA expressed in the liver miR122, thereby the replication of hepatitis c virus.

Of these anti viral drugs, only interferon and ribavarin are used in clinical practise in treating hepatitis c virus.

Ribavarin is not used in chronic kidney disease as it causes haemolytic anaemia.

MANAGEMENT OF CKD PATIENTS INFECTED WITH HEPATITIS C VIRUS

As hepatitis C virus causes various immune complex mediated glomerulonephritis and has an adverse impact on survival of patients on maintenance hemodialysis, it is very important to treat hepatitis C virus HCV infection. The survival of hepatitis C virus infected renal transplant recipients is inferior when compared to renal transplant recipients not infected with hepatitis c virus. The chances of occurrence of de novo glomerulonephritis of the allograft and NODAT is very high.

Thus, it is very important to treat chronic kidney disease patients infected with hepatitis C virus, as it clears the viremia and attainment of sustained viral response.

The important factors that influences the treatment of CKD patients infected with HCV are histology of the liver, patient age, associated co morbidities and the tolerance of patient to anti viral therapy.

Stage of CKD	IFN[a]	Ribavirin[b]	Common adverse events
1 and 2	Pegylated IFN alfa-2a: 180 μg SQ q week Pegylated IFN alfa-2b: 1.5 $\mu g\,kg^{-1}$ SQ q week	800–1200 $mg\,day^{-1}$ in two divided doses	IFN: headache, flu-like illness, depression Ribavirin: worsened anemia due to hemolysis
3 and 4	Pegylated IFN alfa-2a: 135 μg SQ q week Pegylated IFN alfa-2b: 1 $\mu g\,kg^{-1}$ SQ q week	Stage 3: 400–800 $mg\,day^{-1}$ in two divided doses Not recommended for eGFR <50 ml per min per 1.73 m^2	IFN: same as above Ribavirin can cause hemolytic anemia and its use must be supported with increased erythropoietin as needed
5	Pegylated IFN alfa-2a: 135 μg SQ q week Pegylated IFN alfa-2b: 1 $\mu g\,kg^{-1}$ SQ q week	Not recommended	IFN: same as above
5D	Alfa-2a IFN: 3 mU SQ 3 times per week Alfa-2b IFN: 3 mU SQ 3 times per week	Not recommended	IFN: same as above
5T 1–5	Not recommended unless treating fibrosing cholestatic hepatitis or life-threatening vasculitis	Not recommended	IFN has been associated with allograft rejection and failure

eGFR, estimated glomerular filtration rate; IFN, interferon; SQ, subcutaneous; q week, every week.

[a]Patients with genotypes 1 and 4 should receive 48 weeks of IFN therapy if an early viral response is obtained at 12 weeks (>2 log fall in viral titer). Genotypes 2 and 3 should be treated for 24 weeks.

[b]See text for a detailed discussion of ribavirin usage and dosing in patient with CKD Stages 3–5. Patients with genotypes 2 and 3 infection should receive 800 $mg\,day^{-1}$ with Stages 1 and 2 CKD. Patients infected with genotypes 1 and 4 should receive 1000–1200 $mg\,day^{-1}$ with Stages 1 and 2 CKD.

Therapy for HCV infection in CKD patients [(16)].

The National institute of health (NIH) revised their consensus statement from 2002, suggesting that in all hepatitis c virus infected patients liver biopsy is not mandatory before starting anti viral therapy.

Liver biopsy should be done for genotypes 1 and 4 . Liver biopsy is not recommended or genotypes 2 and 3, . Patients with chronic hepatitis with significant fibrosis due to HCV i.e., Metavir score of 2 or more than 2, Ishak scoreof 3 or more than 3) should receive antiviral therapy.

Kdigo guidelines states that hepatitis c virus infected chronic kidney disease patient showing persistent positivity to virus should undergo liver biopsy.

This pre transplant liver biopsy is useful in assessing the severity of injury to the liver and predicting the prognosis and pre transplant and post transplant management.

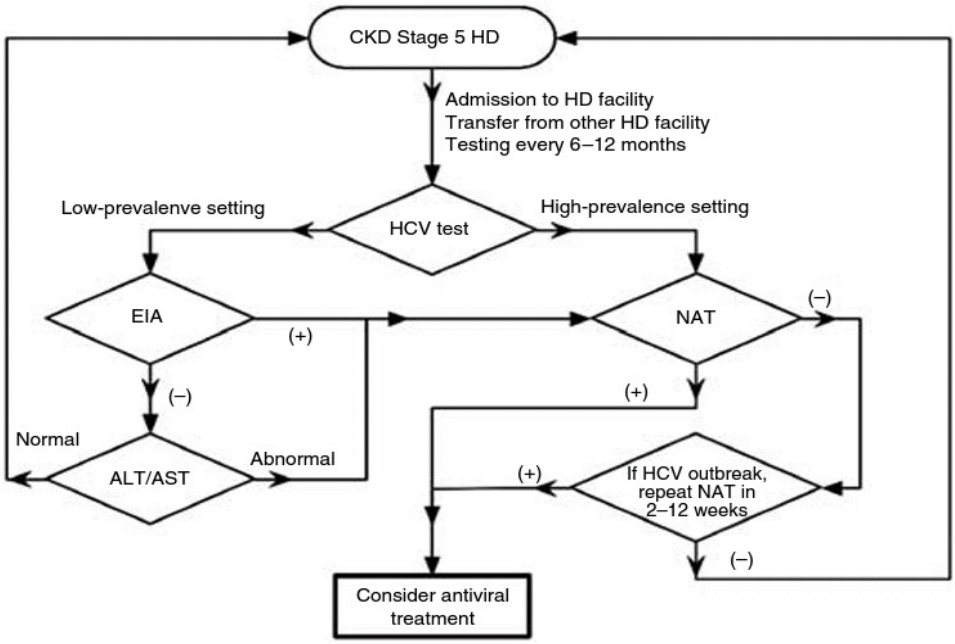
HISTOLOGICAL SCORING SYSTEM OF LIVER FIBROSIS

Stage	Metavir system	Ishak system
0	No fibrosis	No fibrosis
1	Periportal fibrosis expansion	Fibrous expansion of some portal areas, with or without short fibrous septa
2	P-P septae (>1 septum)	Fibrous expansion of most portal areas, with or without short fibrous septae
3	P-C septae	Fibrous expansion of most portal areas with occasional P-P bridging
4	Cirrhosis	Fibrous expansion of portal areas with marked bridging (P-P or P-C)
5	—	Marked bridging (P-P or P-C) with occasional nodules (incomplete cirrhosis)
6	—	Cirrhosis

Adapted from Strader et al [17]

Chronic kidney disease patients can acquire HCV infection by infected blood products transfusion or in hemodialysis unit by hospital related transfusion.

As rate of spontaneous clearance after acute HCV Infection is very low, when compared to general population acquiring acute HCV infection, treatment with antivirals should be started.



CKD Stage 5 hemodialysis diagnostic algorithm[18].

The long term survival of patient and graft of renal transplant recipients with HCV infection is reduced when compared with uninfected renal transplanted recipients.

These recipients can develop acute glomerulopathy, de novo hcv associated nephropathy , new onset of diabetes mellitus after transplantation and severe sepsis. The incidence of chronic allograft nephropathy is increased for these complications, it is very important HCV infected patients planned for renal transplantation.

The current recommendation is that, for these HCV infected patients ant viral therapy should be given even for lesser degree of liver fibrosis(metavir <2 and ishak >3).

When compared to non HCV infected renal transplant recipients , HCV infected renal transplant recipients have poor patient and graft survival. This is due to the development of hepatic and extra hepatitic complications by hepatitis c virus [19].

In 40% of the CKD stage V patients on dialysis patients treated with non pegylated interferon, sustained viral response is attained [20].

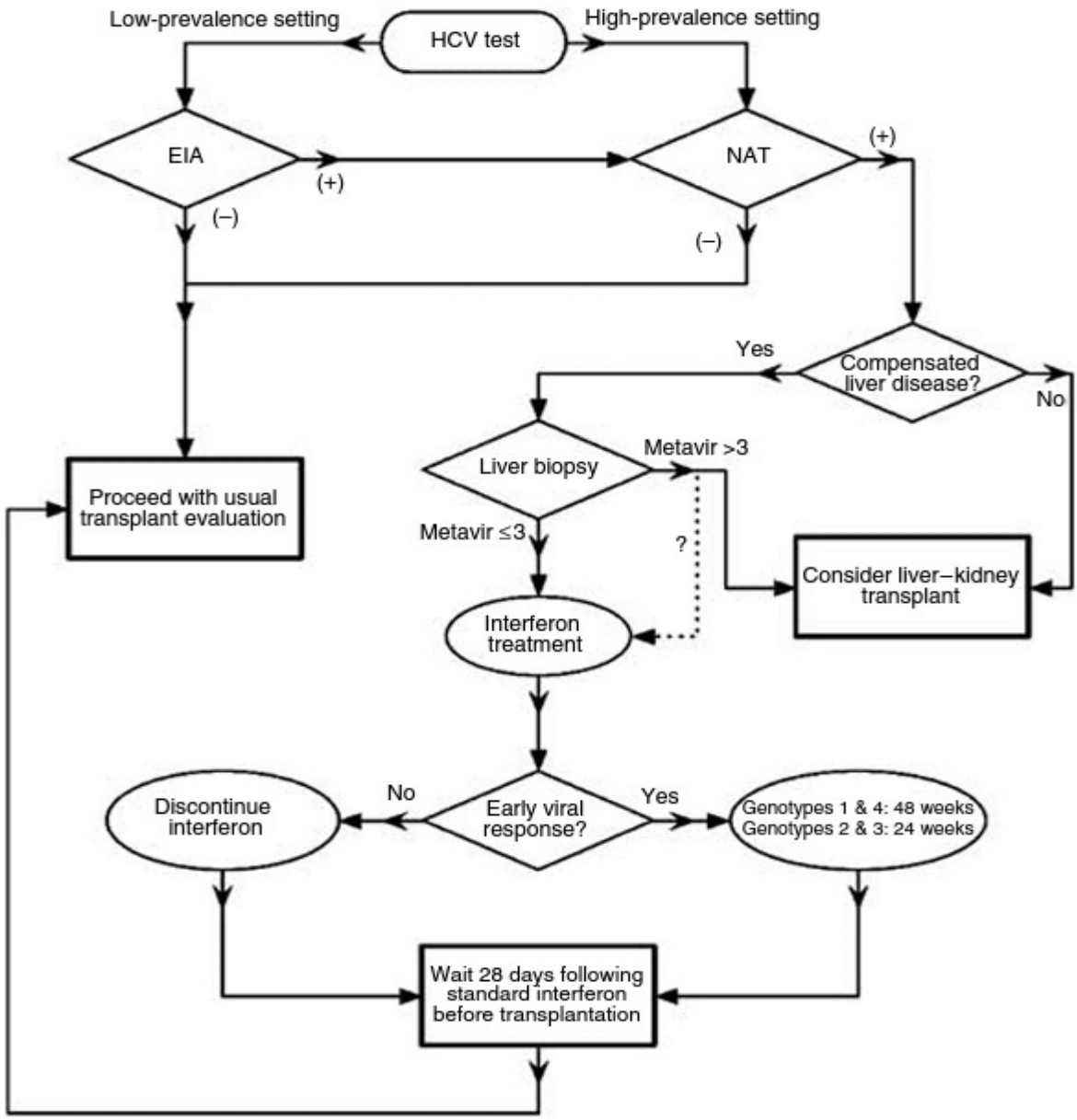
The renal transplant recipients who achieve sustained viral response before transplantation with interferon therapy, the response is sustained in 80-90% of the recipients after transplant [21].

When HCV positive recipients are started on interferon after renal transplantation, there is high chance of graft failure and dysfunction. Interferon increases the antigenicity of the allograft, by increasing the human leukocyte antigen (HLA) class I and II. Interferon decreases the function of suppressor T cells and increases the cytolytic effector immune cell numbers.

Acute rejection caused by interferon therapy can lead to higher incidence of dropouts during antiviral therapy, which is frequently steroid resistant and irreversible.

PRE TRANSPLANTATION EVALUATION OF HEPATITIS C VIRUS INFECTED PATIENTS

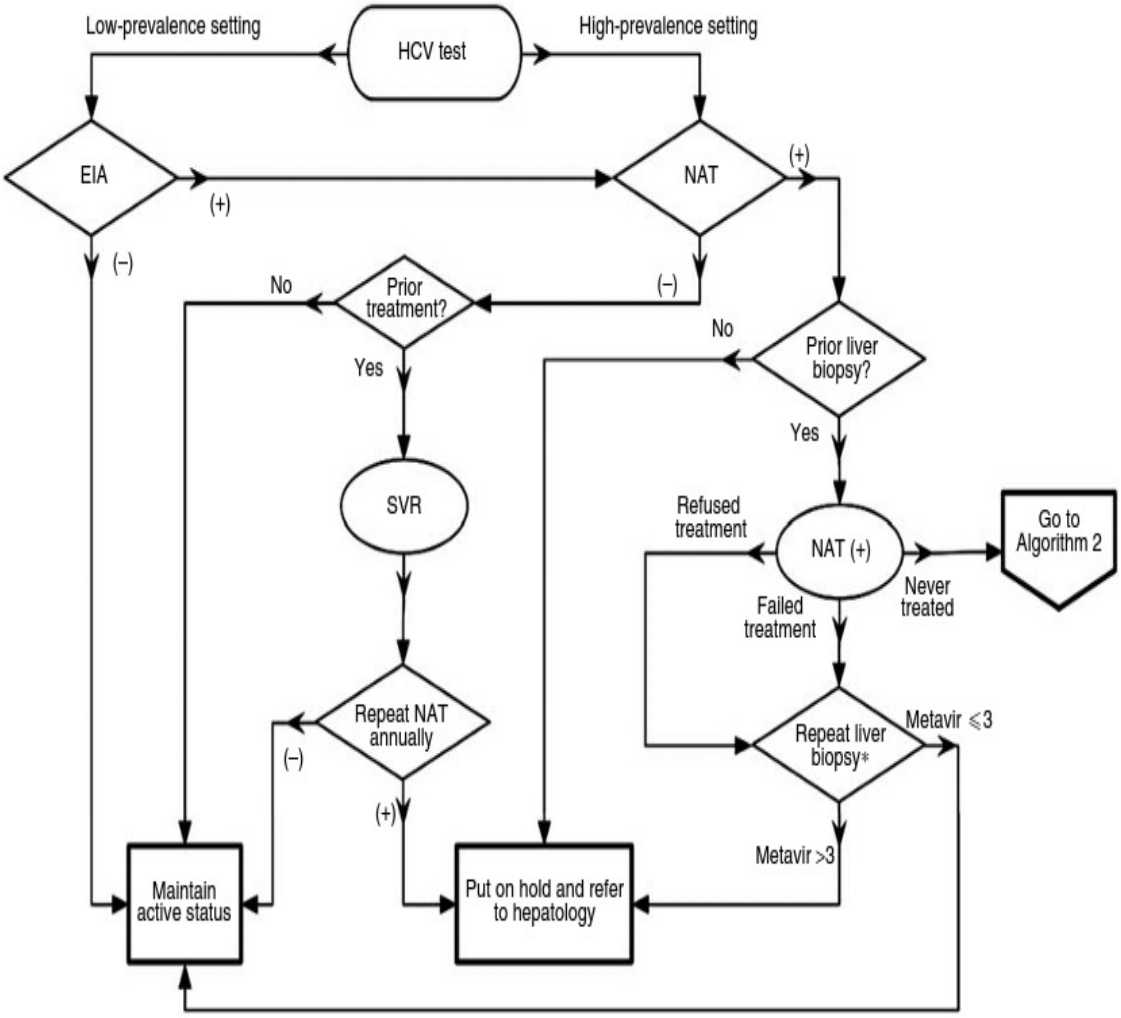
Patients on live related transplant programme or on deceased donor programme should be initially be tested for anti HCV anti bodies by enzyme immunoassay(EIA). Patients who demonstrate detectable anti HCV antibodies should undergo nucleic acid testing (NAT) qualitative or quantitative HCV RNA testing. Patients whose HCV RNA are demonstrated by nucleic acid test should undergo genotype testing.



PRE TRANSPLANT EVALUATION OF HEPATITIS C VIRUS INFECTION [22]

EIA: enzyme immunoassay; NAT: nucleic acid test ;

Early viral Response: patients have a more than 2 log decrease in viral titer.; IFN: interferon;



MANAGEMENT OF THE WAIT-LISTED PRETRANSPLANT CANDIDATE. [23]

NAT: nucleic acid test;

EIA: enzyme immunoassay;

SVR: sustained virologic response

IMMUNOSUPRESSON REGIMENS

Various immunosuppressive agents used during and after renal transplantation has an influence over the kinetics of hepatitis c virus , resulting in differing effects on the replication of virus, progression of the liver disease, various extra hepatic manifestations and the outcomes of the patient and graft.

All current conventional maintenance immunosuppressive agents can be used in renal transplant recipients infected with hepatitis c virus.

Studies have shown that corticosteroid pulses given for acute rejection in HCV infected liver transplanted recipients leads to 100 fold increase in RNA levels , increased episodes of acute hepatitis and earlier occurrence of recurrence of disease.

ANTI VIRAL PROPERTIES OF CYCLOSPORINE

Cyclosprine exerts the anti viral property by inhibiting Cyclophilin B, which is a cofactor for replication of HCV genome in cells. Cyclosporine inhibits the association of cyclophilin B with non structural protein NS5B, thereby suppressing the replication of HCV genome[(24)].

The risk of developing nodat is very high with tacrolimus when compared to cyclosporine, it is advisable to follow cyclosporine based regimen.

Mycophenoloate mofetil has being shown to infect hepatitis C virus replication ,but this is proven only in patients not undergoing renal transplantation only.

Management of hepatitis C virus related complications in kidney. There is no much difference in short term patient survival of hepatitis C virus positive renal transplant recipients. The proposed recommendations in monitoring the occurrence of any liver disease are Monitoring of liver enzymes after renal transplantation monthly for the first six months and then every three months.

Patients with elevation of liver enzymes should be referred immediately to the hepatologist . Liver biopsy should be performed when the liver disease is worsening. Patients with liver biopsy proven cirrhosis should be screened by ultrasound of the liver and alfa feta protein annually to rule out hepatocellular carcinoma.

Management of kidney diseases associated with hepatitis c virus infection. Hepatitis c virus infection can cause various glomerular lesions,even in the absence of significant liver disease and all patients are associated with HCV RNA seropositivity. The various renal involvement due to HCV infection post renal transplant are

- Type I membrano proliferative glomerulo nephritis associated with cryoglobulinemia
- Membrano proliferative glomerulo nephritis not associated with cryoglobulinemia
- Membranous glomerulonephritis
- Focal segmental glomerlosclerosis
- Rapidly progressive renal failure
- Thrombotic microangioathy associated with anti cardiolipin antibodies
- Fibrillary and immunotactoid glomerulopathy.

The hepatitis C virus positive renal transplant recipients developing these glomerular disease present with protienuria and microscopic hematuria and variable impairment of renal function.

In patients with membrano proliferative glomerluonephritis, a very low levels of cryoglobulins (cryokit levels < 3%) containing HCV RNA van be found in 50 % of the patients .when these recipients develop this glomerular involvement , they have acute nephritic syndrome in 25% and nephrotic syndrome in 20% of patients, they also present with hematuria and variable degrees of renal impairment.

Renal biopsy done for these patients with cryoglobulemic membrano proliferative glomerulonephritis demonstrates glomerular immune complex deposition and other findings suggestive of membrano proliferative glomerulonephritis.

The specific renal biopsy finding include precipitation of immune complexes or cryoglobulins as eosinophilic material, vasculitis of small and medium sized renal arteries.

Electron microscopy reveals, usually a sub endothelial immune complex deposition and cryoglobulins deposited in fibrillar or immunotactoid pattern.

The clinical profile of HCV positive renal transplant recipients developing non cryoglobulinemic membrano proliferative glomerulonephritis is similar to that of idiopathic type I membrano proliferative pattern.

In about 80% of hepatitis c virus positive renal transplant recipients, cryoglobulinemia is detected , a higher incidence compared to 40-50% of non renal transplant hepatitis c virus positive patients [25].

The type of cryoglobulinemia is type III 78 %, type II is 22 %[26].

Immunosuppressants given post transplant promotes the viremia of hepatitis C virus to a greater extent and alters the T helper cells 2/ T helper cells 1 balance towards T helper cells 2 response , thus causing cryoglobulinemia.

Immune complexes containing hepatitis C virus proteins has been implicated in the pathogenesis of membrano proliferative glomerulo nephritis.

There is activation of mesangial toll like receptor 3 by immune complexes containing HCV RNA . This activated immune complexes causes the release of various cytokines and chemokines , which affects the proliferation and apoptosis of mesangial cells[27].

Interferon given post transplant increase the risk of development of acute humoral rejection, thus complicating the treatment of membranous nephropathy developing post transplant[28].

Interferon increases the antigenicity of the allograft, by increasing the human leukocyte antigen (HLA) class I and II. Interferon decreases the function of suppressor T cells and increases the cytolytic effector immune cell numbers.

In 50-100% of interferon treated renal transplant recipients , risk of developing rejection is increased[29].

The only indications were interferon can be given post transplant are fibrosing cholestasis and life threatening vasculitis.

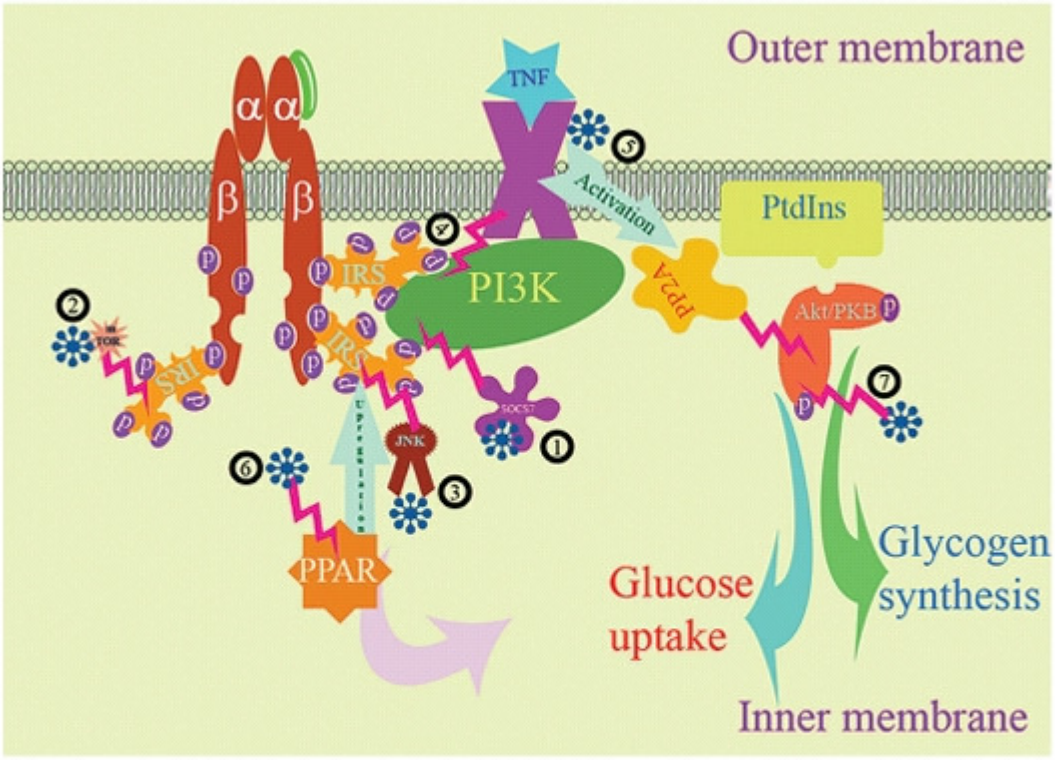
Ribavarin reduces the viral load and decreases the formation of immune complexes . But ,ribavarin increases the viral load and worsens the liver function when given in the absence of antiviral therapy.

Rituximab improves the renal function and decreases the cryoglobulinemia when given to hepatitis c virus positive renal transplant recipients[30][31].

The recommendation is to screen for for protienuria, hematuria and estimated glomerular filtration rate annually to diagnose renal diseases caused by hepatitis C virus.

NEW ONSET OF DIABETES MELLITUS AFTER RENAL TRANSPLANTATION(NODAT)

Hepatitis c virus has been implicated in the causation of new onset of diabetes mellitus after renal transplantation. This occurs in the early period after transplant. The exact pathogenic mechanism for this development is incompletely understood . The possible mechanism include



Schematic representation of some of the effects induced by hepatitis C virus (HCV) on insulin signaling in hepatocytes. It has been shown that HCV interferes with the insulin pathway at multiple nonexclusive levels: the HCV core can activate inhibitors of insulin signaling including (1) the suppressor of cytokine signaling-7 (SOCS-7), (2) mammalian target of rapamycin (mTOR), and (3) c-Jun N-terminal kinase (JNK). Increased secretion of tumor necrosis factor (TNF)-α by the HCV suppress IRS-1 activation of phosphatidylinositol 3 (PI3)-kinase (4) and activation of the protein phosphatase 2A (PP2A) inhibits Akt (5). HCV also downregulates IRS-1 through inactivation of PPAR (6) and inactivates Akt by downregulating its phosphorylation (7).

Contribution of Hepatitis C Virus and NODAT [32]

INSULIN RESISTANCE :

This is the predominant pathogenic mechanism in causing NODAT. Hepatitis c virus causes diminished signalling through insulin receptor . this has been proven from biopsy specimens taken from liver of hepatitis c virus positive patients[33].

DECREASED GLUCOSE UPTAKE BY LIVER

Hepatitis c virus core protein suppresses insulin mediated glucose uptake by the liver. The evidence comes from studies with hepatoma cells of human [34].

DECREASED INSULIN SECRETION

HEPATITIS C VIRUS PANCREATIC BETA ISLET CELL CYTOPATHY- studies have demonstrated staining of hepatitis c virus in pancreatic beta islet cells resulting in decreased insulin secretion on stimulation by glucose.

IMMUNE MEDIATED (MOLECULAR MIMICRY) has been proposed but this has not been proven by any studies[35].

DECREASED HEPATIC GLYCOGENESIS

The expression of hepatitis c virus polyprotein inhibits post receptor pathway of insulin , thereby inactivates glycogen synthase activity. This has been proven by studies with human hepatic cell line[36].

The expression of insulin receptors and insulin receptor pathway is increased in Hepatitis c virus infected patients when compared with hepatitis c virus uninfected patients , but the downstream signalling through phosphoinositide-3 kinase was decreased in liver cells of hepatitis c virus infected individuals. So, the defect is beyond the insulin receptor contributing to the insulin resistance and impairment of the glucose metabolism [37].

The meta analysis by Fabrizi et al, has shown that the seropositivity of hepatitis c virus confers a 3.75 fold increased risk of NODAT in renal transplant recipients [38].

The presence of HCV infection was associated with 62 % increase in risk of insulin resistance. A 10 fold increase in HCV RNA levels was associated with 8% increased risk for insulin resistance. The study by Kamar et al has shown that when hepatitis c virus patients are treated with interferon before transplant , the risk of development of NODAT is decreased [39].

IMPACT OF HEPATITIS C VIRUS ON RENAL TRANSPLANTATION

Meta analysis of eight clinical trails by Fabrizi et al, out of which six were cohort studies and two were controlled studies comparing the outcomes of renal transplantation among hepatitis c virus positive and hepatitis C virus negative recipients , reveal that adjusted relative risk of mortality was 1.79 with a confidence interval of 1.57 -2.03 in hepatitis c virus positive recipients. This increased mortality is due to increased frequency of hepatocellular carcinoma and liver cirrhosis. There is an adjusted relative risk of graft loss of 1.56 with a confidence interval of 1.35 -1.80.This increased graft loss is due to increased occurrence of de novo immune mediated glomerular lesions, especially type I membrano proliferative glomerulonephritis post transplant [(40)].

The study by Rostami et al, analysed 18 observational studies , out of which 16 were retrospective cohort studies and 2 were clinical trials. In this study , the combined hazard ratio for mortality of hepatitis c virus positive recipients compared to hepatitis c virus negative recipients was 1.69 times (1.33-1.97, $p<0.0001$) and graft loss was 1.56 fold (1.22-2.004) [(41)].

The study by Jose Mario Morales et al, comparing the various clinical outcomes of hepatitis C virus infected renal transplant recipients and hepatitis c virus non infected renal transplanted recipients. This study

revealed that 4 year survival of the graft in HCV infected recipients was 89.5% and HCV uninfected recipients was 94.4% , p <0.005. The survival of the patient in hepatitis infected recipients was 94.5% and HCV uninfected recipients was 96.6%, p<0.05. The incidence of acute rejection, severe proteinuria, de novo glomerular disease was high in HCV infected renal transplanted recipients[42].

The study by S K Agarwal et al, compared hepatitis C virus infected and hepatitis C virus .The follow up period was 30 months. During this follow up, the patient survival was 72% in hepatitis C virus infected group and 66% in hepatitis C virus uninfected group (statistically not significant). The allograft survival was 72% in hepatitis C virus infected group and 66% in hepatitis C virus infected group and 66% in hepatitis C virus uninfected group (statistically not significant) [43].

The incidence of acute rejection in HCV positive recipients was 32.5% , in HCV negative recipients was 27.3%. [44]

Studies by Morales et al and Rao et al , have shown that hepatitis c virus positive patients have frequent blood stream infections like cytomegalovirus and sepsis. [45],[46]

RESULTS

A total of 266 patients underwent renal transplantation between 2010 and 2013. Three patients were detected hepatitis C virus infection after transplantation . These three patients were excluded from the study. Out of the 263 patients, 28 recipients who had hepatitis C virus infection before transplant were included in the study, the clinically significant outcomes like acute rejection, NODAT, sepsis, cytomegalo virus infection , interstitial fibrosis and tubular atrophy (IFTA) were compared with 235 recipients whose serology were negative for hepatitis C virus.

Retrospective and prospective study of transplant profile of 28 recipients who had hepatitis c virus before transplant were studied in detail, the results are summarised as :

- The mean duration of follow up was 23 months.
- Of the 28 recipients , 19 were males with male: female ratio of 2.1:1.
- Mean age of the study population was 34 years(14-45 years).
- Live related donor transplant was done in 23 patients (82%).
- Deceased donor transplant was done in 5 patients (18%) .
- Elevation of liver enzymes was present in 4 patients(14 %).

- Hepatitis C virus RNA was detectable in 5 patients (18%) .
- Out of 28 patients, only one patient (3.5%) received interferon for six months before transplant.
- All the patients were started on triple immunosuppression of prednisolone, cyclosporine and mycophenoloate mofetil.
- Out of the 5 deceased transplant recipients , 3(60%) were given induction agents with basiliximab.
- Delayed graft function was present in 11(39%) patients.
- Acute cellular rejection was present in 8 patients (26%) and were treated with pulse methyl prednisolone.
- New onset of diabetes mellitus after transplant (NODAT) was present in 16 patients (57%). All patients developed NODAT within 3 months.
- Sepsis (clinical evidence of sepsis and microorganism demonstrated by blood culture or urine culture) occurred in 17 recipients (61%).
- Cytomegalovirus infection was present in 11 recipients (39%).
- Invasive fungal infection was present in 7 recipients (25%).Biopsy done in 19 recipients (68%) revealed,

Findings	Number
Acute tubular injury	7
Acute cellular rejection	8
Calcineurin inhibitor toxicity	7
Interstitial fibrosis and tubular atrophy	9
Thrombotic microangiopathy	1
Transplant glomerulopathy	1
Focal segmental glomerulosclerosis	1

Post transplant worsening of liver function was present in 5 (18%) recipients, 4 (14%) among them had elevation in HCV RNA level .

Liver biopsy was done in 1 recipient (3.5%) findings were:

CHRONIC HEPATITIS: Ishak modified hepatitis index inflammatory scale (HAI) 4/118, fibrosis 2/6.

The clinical outcome of the one recipient (3.5%) treated with interferon pretransplant was better, there was no progression of liver disease.

Two recipients (7%) developed graft artery thrombosis in the post operative period and graft nephrectomy was done to both recipients and became dialysis dependent.

Interferon was given to one post graft nephrectomy recipient (3.5%) who developed worsening of liver function and massive elevation of HCV RNA titers.

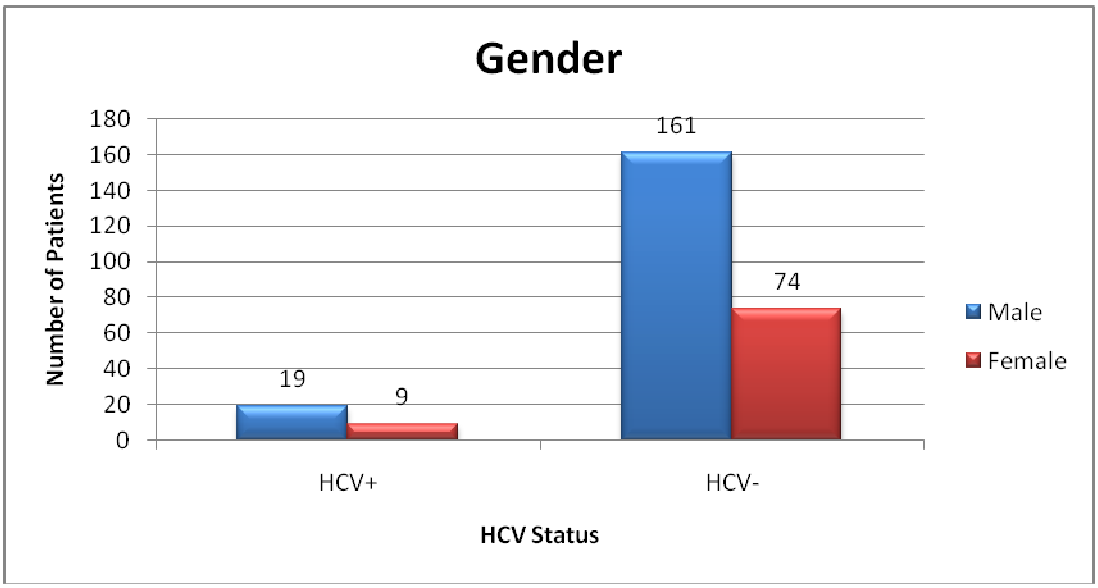
All recipients underwent alpha seum feto protein test yearly , no recipient showed clinical or biochemical evidence of hepatocellular carcinoma.

Routine urine examination revealed protienuria in one patient (3.5%), for whom biopsy was done which revealed focal segmental glomerulosclerosis.

One recipient (3.5%) expired due to sepsis 20 days following transplant, one year patient survival rate in HCV positive recipients was 96.43%.

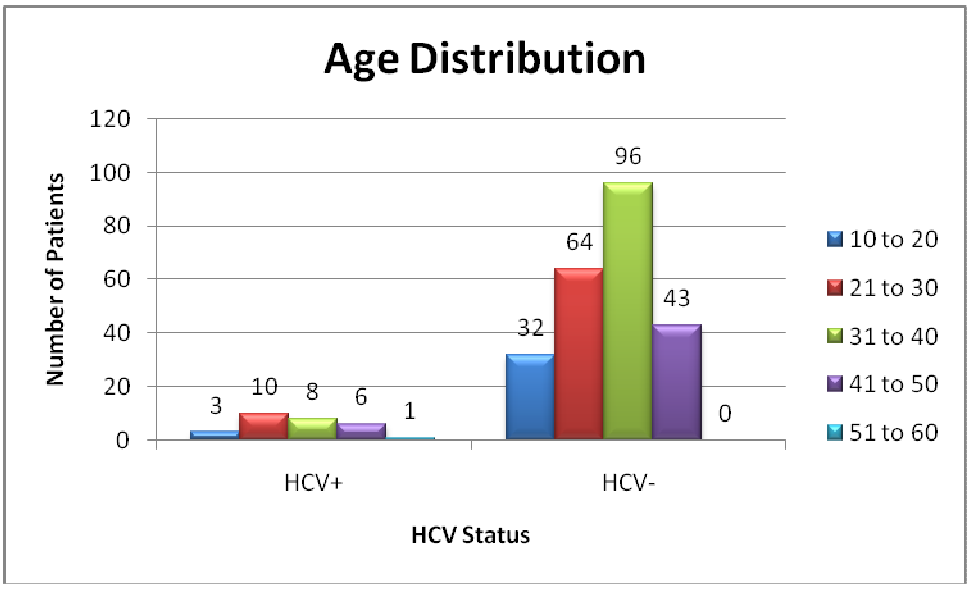
On follow up, 3 recipients became dialysis dependent (10.71%). Normal graft function was present 15 recipients (54%), with mean s.creatitine of0.9mg/dl.

GENDER



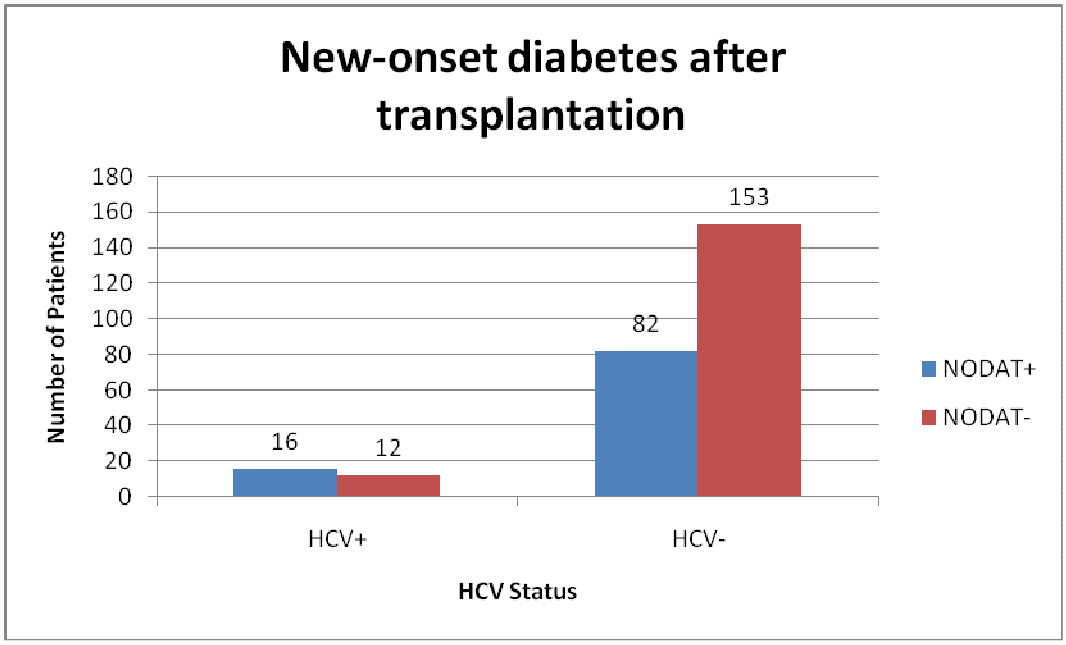
Gender Distribution	HCV+	%	HCV-	%
Male	19	67.86	161	68.51
Female	9	32.14	74	31.49
Total	28	100	235	100
P value	**0.9439**			

AGE



Age	HCV+	%	HCV-	%
10 to 20	3	10.71	32	13.63
21 to 30	10	35.71	64	27.27
31 to 40	8	28.57	96	40.90
41 to 50	6	21.43	43	18.20
51 to 60	1	3.57	0	0.00
Total	28	100	235	100

NODAT

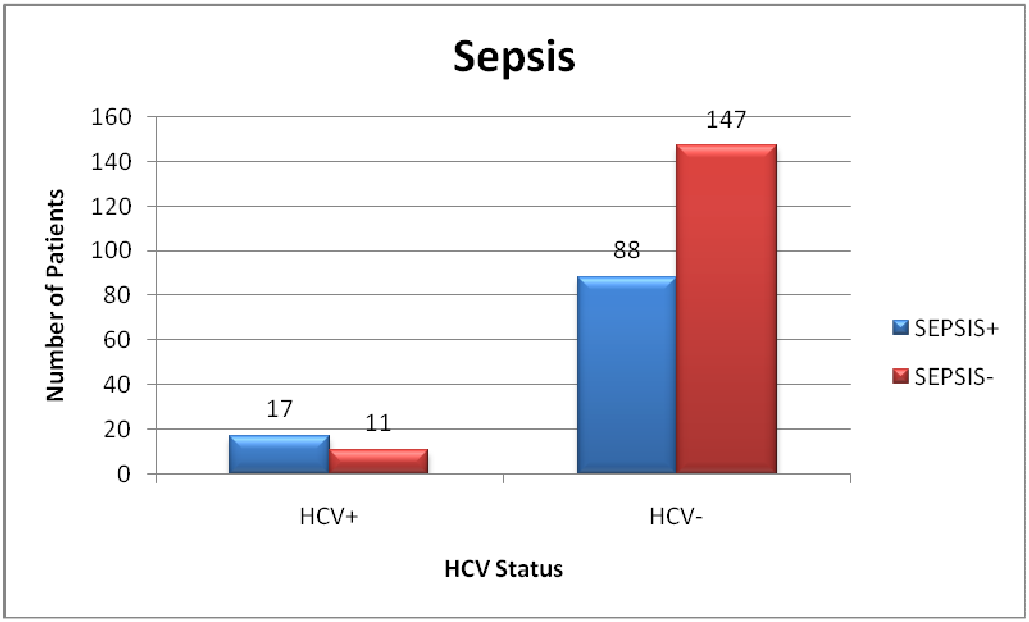


NODAT	HCV+	%	HCV-	%
NODAT+	16	57.14	82	34.89
NODAT-	12	42.86	153	65.11
Total	28	100	235	100
Hazard Ratio	**2.4878**			
95% CI	**1.1233 to 5.5097**			
RR	**2.2449**			
P value	**0.0247***			

The incidence of NODAT in HCV positive recipients was 57.14%, in HCV negative recipients was 34.89%. This difference was statistically significant (p = 0.0247).

The HCV positive recipients has 2.24 fold increased risk of developing NODAT (H.R. **2.4878 with CI of 1.12 to 5.5).**

SEPSIS

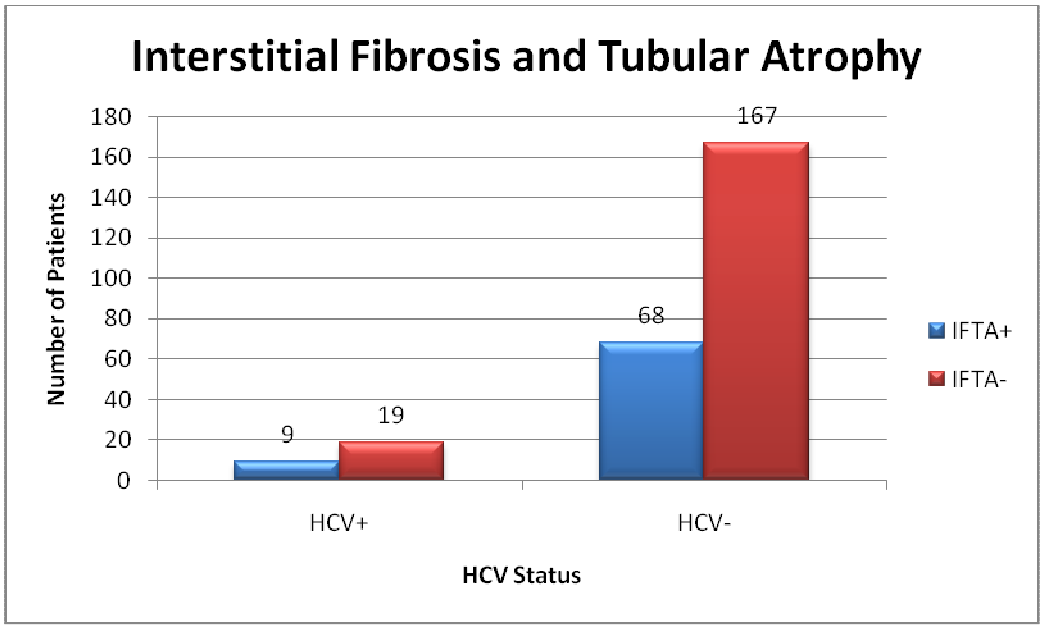


SEPSIS	HCV+	%	HCV-	%
SEPSIS+	17	60.71	88	37.45
SEPSIS-	11	39.29	147	62.55
Total	28	100	235	100
Hazard Ratio	**2.5816**			
95% CI	**1.1564 to 5.7634**			
RR	**2.3255**			
P value	**0.0206***			

The incidence of sepsis in HCV positive recipients was 60.71%, in HCV negative recipients was 37.45%. This difference was statistically significant (p=0.026).

The HCV positive recipients were 2.32 fold higher risk of developing sepsis (2.58 with CI 1.15 TO 5.76).

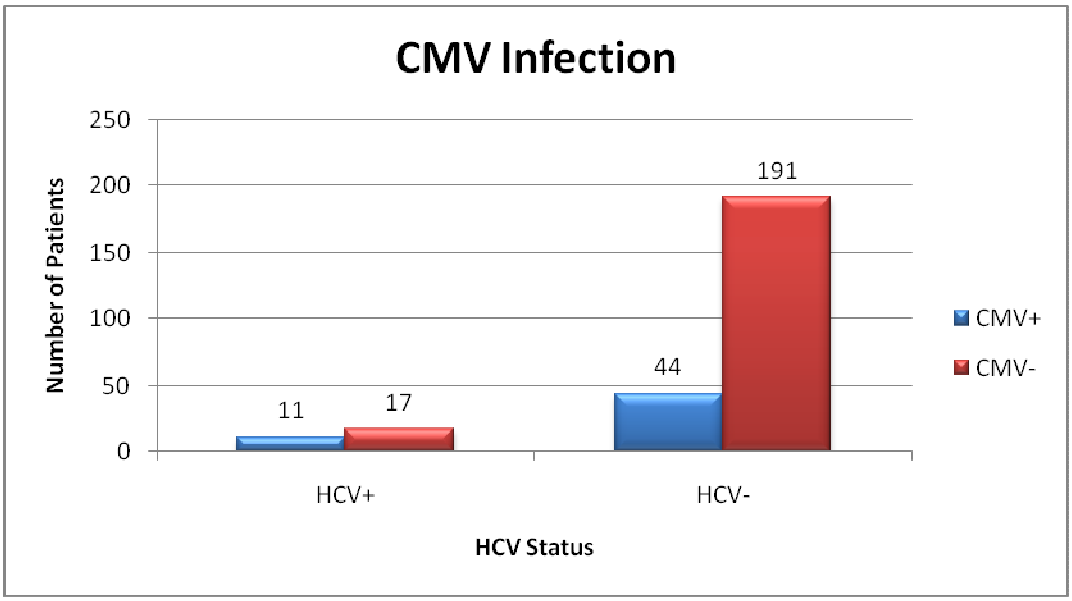
IFTA



IFTA	HCV+	%	HCV-	%
IFTA+	9	32.14	68	28.94
IFTA-	19	67.86	167	71.06
Total	28	100	235	100
Hazard Ratio	**1.1633**			
95% CI	**0.5013 to 2.6994**			
RR	**1.1442**			
P value	**0.7247**			

The incidence of IFTA in HCV positive recipients were 32.14%, in HCV negative recipients were 28.94%. This incidence was not statistically significant, p=0.7247.

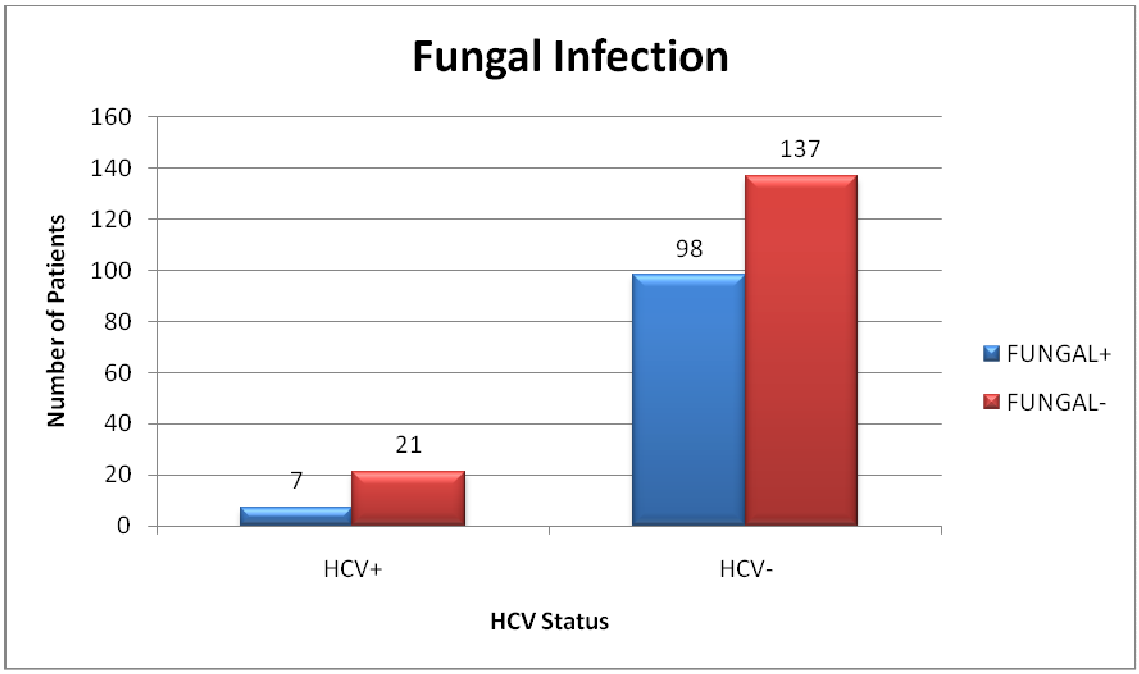
CMV INFECTION



CMV	HCV+	%	HCV-	%
CMV+	11	39.29	44	18.72
CMV-	17	60.71	191	81.28
Total	28	100	235	100
Hazard Ratio	**2.8088**			
95% CI	**1.2294 to 6.4172**			
RR	**2.7723**			
P value	**0.0143***			

The incidence of Cytomegalovirus in HCV positive group 39.29%, in HCV negative group was 18.72%. This difference was statistically significant, p= 0.0148. The HCV positive group had 2.8 fold of developing CMV infection when compared with HCV negative group, with hazard ratio of **2.8088 with C.I. of 1.2294 to 6.4172.**

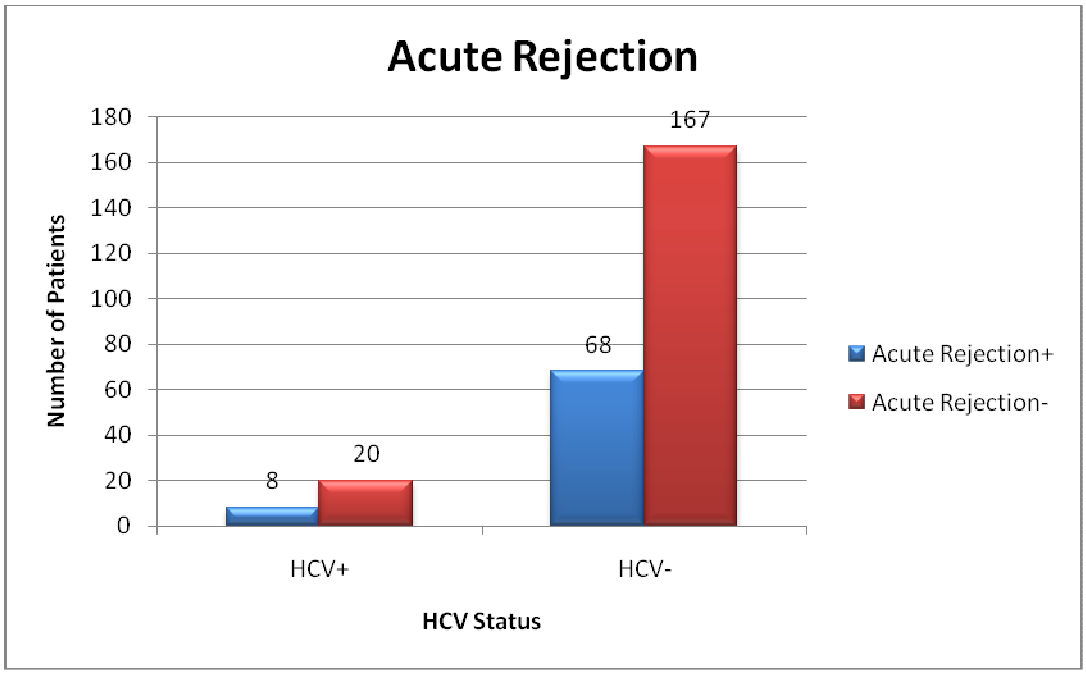
FUNGAL INFECTION



Fungal Infection	HCV+	%	HCV-	%
FUNGAL+	7	25.00	98	41.70
FUNGAL-	21	75.00	137	58.30
Total	28	100	235	100
Hazard Ratio	**0.4660**			
95% CI	**0.1906 to 1.1391**			
RR	**0.5016**			
P value	**0.0941**			

The incidence of fungal infection in HCV positive recipients was 25%, in HCV negative recipients was 41.7%, this difference was not statistically not significant, p=0.0941.

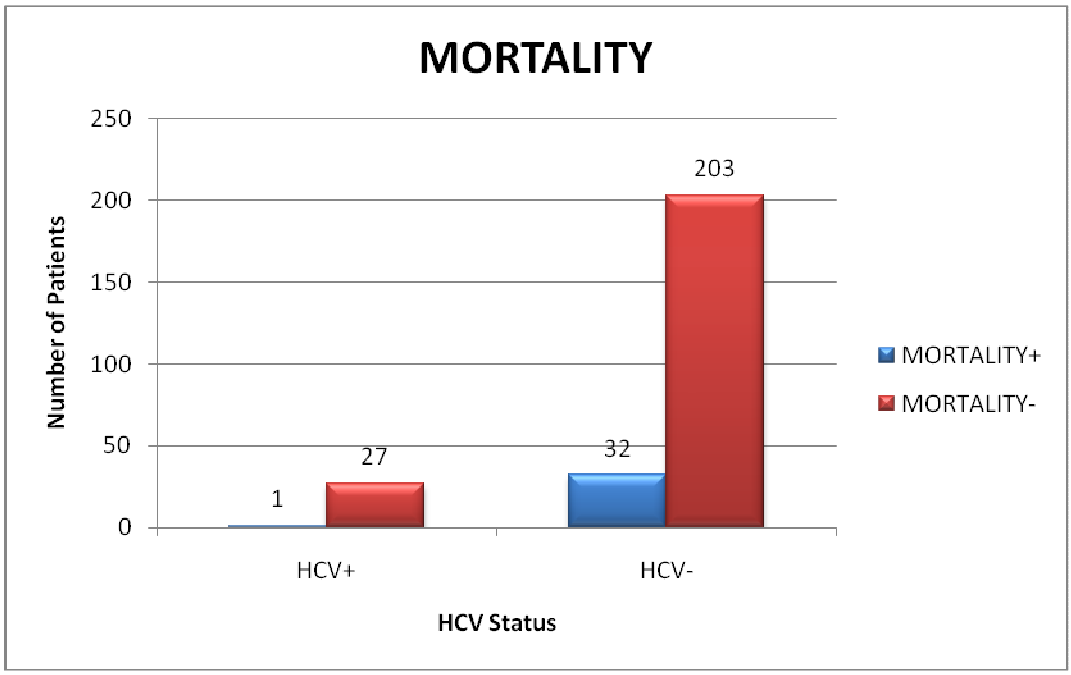
ACUTE REJECTION



Acute Rejection	HCV+	%	HCV-	%
Acute Rejection+	8	28.57	68	28.94
Acute Rejection-	20	71.43	167	71.06
Total	28	100	235	100
Hazard Ratio	**0.9824**			
95% CI	**0.4128 to 2.3379**			
RR	**0.9842**			
P value	**0.9679**			

The incidence of acute rejection in HCV positive recipients was 28.57%, in HCV negative recipients was 28.575, this difference was statistically insignificant, p=0.9679.

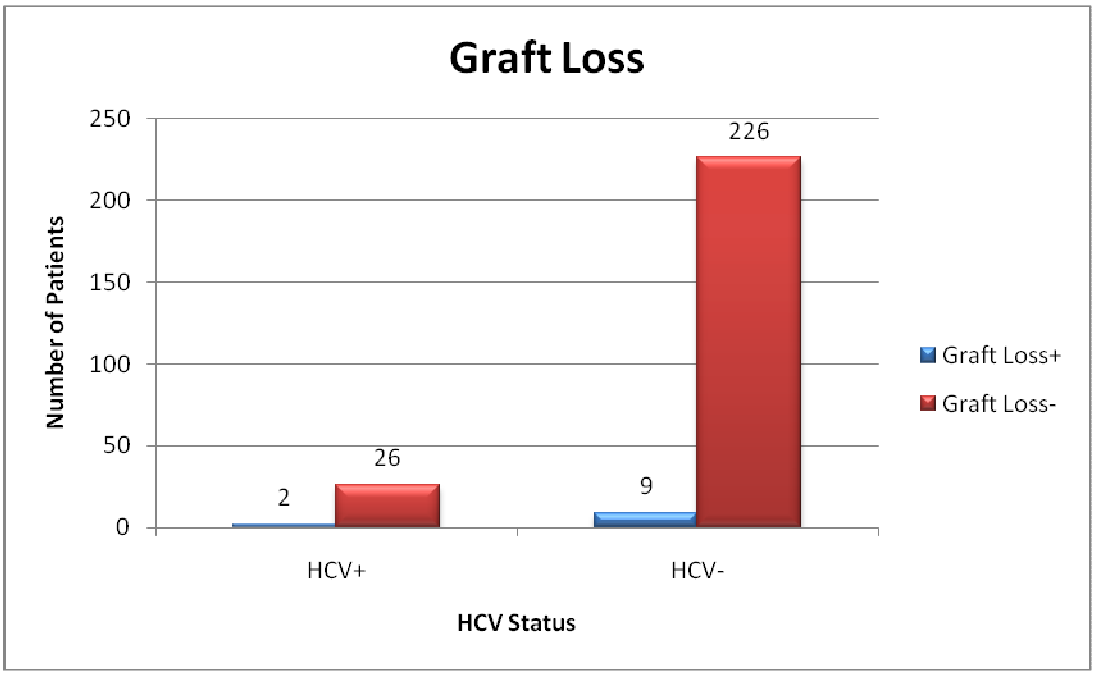
MORTALITY



MORTALITY	HCV+	%	HCV-	%
MORTALITY+	1	3.57	32	13.62
MORTALITY-	27	96.43	203	86.38
Total	28	100	235	100
Hazard Ratio	**0.235**			
95% CI	**0.0308 to 1.17898**			
RR	**0.2581**			
P value	**0.1621**			

The incidence of mortality in HCV positive group was 3.57% , in HCV negative recipients was 13.62%, this difference was statistically insignificant, p=0.1621.

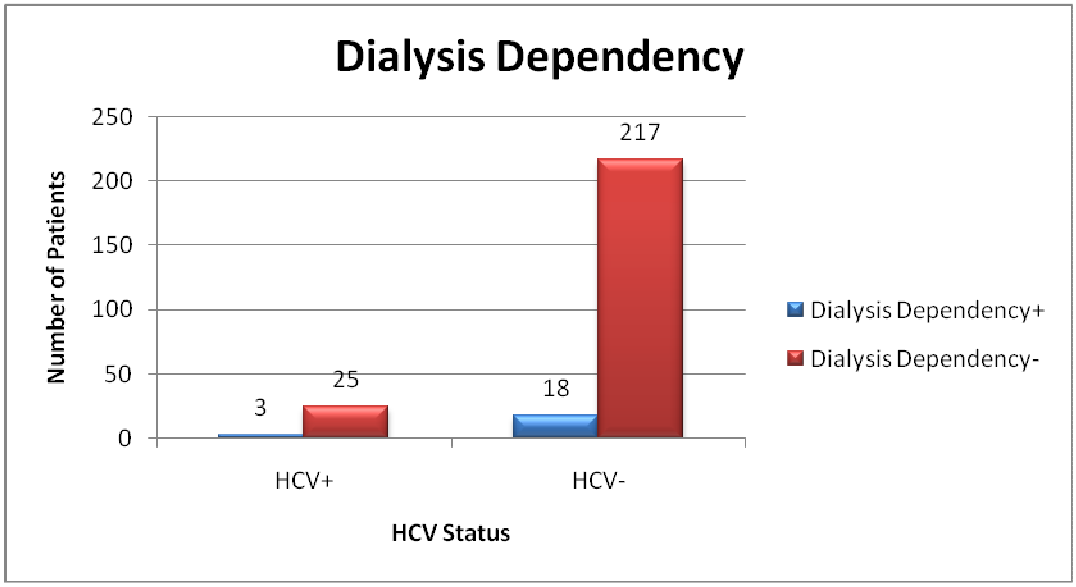
GRAFT LOSS



Graft Loss	HCV +	%	HCV-	%
Graft Loss+	2	7.14	9	3.83
Graft Loss-	26	92.86	226	96.17
Total	28	100	235	100
Hazard Ratio	**1.9316**			
95% CI	**0.3959 to 9.4255**			
RR	**1.7622**			
P value	**0.4156**			

The incidence of graft loss in HCV positive recipients was 7.14%, in HCV negative recipients was 3.83 %, this comparison was statistically insignificant, p=0.4156.

DIALYSIS DEPENDENCY



Dialysis Dependency	HCV+	%	HCV-	%
Dialysis Dependency+	3	10.71	18	7.66
Dialysis Dependency-	25	89.29	217	92.34
Total	28	100	235	100
Hazard Ratio	**1.4467**			
95% CI	**0.3989 to 5.2579**			
RR	**1.3829**			
P value	**0.5749**			

The incidence of dialysis dependency in HCV positive recipients was 10.7%, in HCV negative recipients was 7.665, this comparsion was statistically insignificant ,p= 0.5749.

DISCUSSION

In our study ,the mortality rate in HCV positive recipients was 3.57% and adjusted relative risks for mortality was 0.235 with C.I. of 0.03 to 0.18. Hepatitis C virus positivity did not confer any increased risk of mortality and graft loss when compared to hepatitis C virus negative recipients.

Meta analysis of eight clinical trials by Fabrizi et al, comparing the outcomes of renal transplantation among hepatitis C virus positive and hepatitis c virus negative recipients , revealed that adjusted relative risk of mortality was 1.79 with a confidence interval of 1.57 -2.03 in hepatitis C virus positive recipients. There was an adjusted relative risk of graft loss of 1.56 with a confidence interval of 1.35 -1.80 [(40)].

Rostami et al, reviewed 18 observational studies. They concluded that the combined hazard ratio for mortality of hepatitis C virus positive recipients compared to hepatitis C virus negative recipients was 1.69 times (1.33-1.97, $p<0.0001$) and graft loss was 1.56 fold (1.22-2.004). [(41)]

In another study by S K Agarwal, hepatitis C positive recipients and hepatitis C virus negative recipients were followed up for a period of 30 months. The patient survival and graft survival was similar [43].

In our study, the hepatitis C virus positive recipients had 2.24 fold increased risk of developing NODAT(H.R. 2.4878 with CI of 1.12 to 5.5). The meta analysis by Fabrizi et al , has shown that the seropositivity of hepatitis C virus confers a 3.75 fold increased risk of NODAT in renal transplant recipients[40].

The hepatitis C virus positive recipients had 2.32 fold higher risk of developing sepsis. The hepatitis C virus positive recipients had 2.8 fold of developing cytomegalovirus infection when compared with hepatitis C virus negative recipients.

Rao K et al, analyzed the incidence of sepsis and cytomegalovirus infection among hepatitis C positive recipients and hepatitis C negative recipients. They have shown that hepatitis C positive recipients had a 1.8 fold increase in incidence of sepsis and cytomegalovirus infection when compared to negative recipients [46].

Studies by Morales et al and Rao et al , have shown that hepatitis C virus positive patients have frequent blood stream infections like cytomegalovirus and sepsis [45] [46].

According to the study by Morales et al, the incidence of acute rejection in HCV positive recipients was 32.5%, in HCV negative recipients was 27.3% [44]. In our study the incidence of acute rejection in HCV positive and negative recipients was similar.

CONCLUSION

The short term patient and graft survival of HCV positive recipients was better.

There was high incidence of NODAT in HCV positive recipients, and occurrence of NODAT was within 3 months after transplant.

The incidence of sepsis and cytomegalovirus in HCV positive recipients was higher, it is better to keep minimal level of immunosupression.

The incidence of acute rejection, interstitial fibrosis, fungal infection and graft survival in HCV positive recipients was not statistically significant from HCV negative recipients.

The short duration of follow up is a main limitation of the study.

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சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு : டெங்குடிஸ் சிவைரஸ் பாதித்த சிறுநீரக நோயாளர்களுக்கு செய்யப்படும் மாற்று சிறுநீரை சிகிச்சை குறித்து ஆய்வு

ஆராய்ச்சி நிலையம் : சிறுநீரக இயல் பகுதி
சென்னை மருத்துவக் கல்லூரி
சென்னை-600 003.

பங்கு பெறுபவரின் வயது :

பங்கு பெறுபவரின் எண் :

பங்கு பெறுபவர் இதனை ( ) குறிக்கவும்.

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது.என்னுடைய சந்தேகங்களை கேட்கவும், அதற்கான தகுந்த விளக்கங்களை பெறவும் வாய்ப்பளிக்கப்பட்டது. ☐

நான் இவ்வாய்வில் தன்னிச்சையாகதான் பங்கேற்கிறேன். எந்த காரணத்தினாலோ எந்த கட்டத்திலும் எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவவாய்வில் இருந்து விலகி கொள்ளலாம் என்றும் அறிந்துக் கொண்டேன். ☐

இந்த ஆய்வின் சம்பந்தமாகவோ, இதை சார்ந்த மேலும் ஆள்வு மேற்கொள்ளும போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தெவையில்லை என அறிந்து கொள்கிறேன். நான் ஆள்வில் இருந்து விலகிக் கொண்டாலும் இது பொருந்தும் என அறிகிறேன். ☐

இந்த ஆய்வின் மூலம் கிடைக்கும் தகவல்களையும், பரிசோதனை முடிவுகளையும் மற்றும் சிகிச்சை தொடர்பான கவல்களையும் மருத்துவர் மேற்கொள்ளும் ஆள்வில் பயன்படுத்திக் கொள்ளவும் அதை பிரசுரிக்கவும் என் முழு மனதுடன் சம்மதிக்கிறேன். ☐

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன். எனக்கு கொடுக்கப்பட்ட அறிவுரைகளின்படி நடந்த கொள்வதுடன் இந்த ஆய்வை மேற்கொள்ளும மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கின்றேன். ☐

பங்கற்பவரின் கையொப்பம் ..... இடம்..... தேதி:

கட்டைவிரல் ரேகை

பங்கற்பவரின் பெயர் மற்றும் விலாசம்;.....

ஆய்வாளரின் கையொப்பம்:..... இடம்..... தேதி.....

PROFORMA

Name: Age: Sex: NC No.:

Occupation:

PRE TRANSPLANT PROFILE:

1.Native kidney disease

2. Duration of Chronic Kidney Disease

3.Duration of dialysis prior to transplant

4..History of blood transfusion

5. History of Jaundice

6.History of Cardiovascular disease

7.Viral Serology - HCV /HBV /HIV

HCV —ELISA ----QUALITATIVE PCR

8.HCV RNA LOAD ----Initial

----Final

9.Treated with interferon -- yes/no

If yes -dose and duration

10.LFT

S.bilirubin(d)

(indirect)

S. protein (t)

S.albumin

S.globulin

SGOT

SGPT

ALP

TRANSPLANT PROFILE :

1. Date of transplant
2. Donor - Live/Cadaver

   Donor age sex
3. INDUCTION AGENT
4. IMMUNOSUPPRESION
5. ACUTE REJECTION
6. ANTI REJECTION THERAPY
7. GRAFT DYSFUNCTION- early/ late
8. NODAT
9. POST TRANSPLANT CHRONIC LIVER DISEASE
10. POST TRANSPLANT HCV RNA STATUS
11. PROTEINURIA
12. POST TRANSPLANT INFECTIONS

    Blood C/S

    Urine C/S

    Cytomegalovirus

    Invasive fungal infections

    Others
13. THROMBOTIC MICROANGIOPATHY(biopsy proven)
14. FIBROSING CHOLESTASIS
15. CRYOGLOBULINEMIA
16. POST TRANSPLANT INTERFERON
17. LFT

    S.bilirubin (d)

    (indirect)

    S. protein (t)

    S.albumin

    S.globulin

SGOT

SGPT

ALP

18. RENAL BIOPSY

19. LIVER BIOPSY

20. DEATH

Cardiovascular

Hepatic failure

Infections

Cancer

Other

INVESTIGATIONS:

1. Urine analysis

Protein

Sugar

Deposits

P.C.R.

2. Hemogram

Hemoglobulin (gm/dl)

Total count

Differential count

E.S.R.

3. Peripheral Smear

4. Blood Urea (mg/dl)-

S.Creatinine(mg/dl)-

S.Electrolytes (mEq/l)-

5. Blood sugar (mg/dl)

6. LFT

S.BILIRUBIN

Direct

Indirect

SGOT

SGPT

S.PROTEINS

ALBUMIN

GLOBULIN

7. PT/INR

8. VIRAL SEROLOGY - HCV/HBV/HIV

9. HCV RNA LOAD

10. CHEST X RAY

11. ULTRASOUND ABDOMEN

12.UPPER GASTRO INTESTINAL ENDO SCOPY

13.RENAL BIOPSY

14. LIVER BIOPSY

FINAL DIAGNOSIS

MASTER CHART

S. No.	NC No.	AGE	SEX	NKD	PRE TRANSPLANT				HCV RNA IU/ML	PRE Tx IFN	DATE OF Tx	DONOR	INDUCTION	IMM SUPP.	DGF	D/W S.Cr. mg/dl	REJECTION	A.R.T.	NODAT	GDF	Other Infections	
					CKD DUR	HD DUR	HCV+ DU	OT, PT														
1	3657/10	19	m	cgn	10m	8m	3m	18,22	nil	no	4/26/2011	mother	no	csa,mmf	yes	1.7	no	no	nil	8m		15m cmv
2	4359/10	29	m	?cgn	15 m	9m	5m	16,32	nil	no	7/19/2011	mother	no	csa,mmf	no	1.2	no	no	nil	6m		
3	5747/10	43	m	?fsgs	8m	5m	2m	16,18	nil	no	5/4/2011	sister	no	csa,mmf	no	1.2	no	no	3 m	8m		
4	876/11	23	m	nk	8m	6m	3m	24,28	nil	no	11/22/2011	father	no	csa,mmf	no	1.2	no	no	2m	16m	4m cmv	
5	3032/09	29	m	nk	10m	8m	3m	16,20	nil	no	12/2/2011	sister	no	csa,mmf	no	0.9	no	no	nil	no	3m candida	
6	1747/11	42	m	nk	12m	9m	4m	20,26	nil	no	12/15/2011	mother	no	csa,mmf	yes	0.9	2a 16d	16d	3m	6m	4 m cmv	
7	1706/10	28	m	nk	8m	6m	2m	24,28	nil	no	3/29/2011	mother	no	csa,mmf	no	0.9	no	no	nil	no		7m candida
8	1260/11	14	f	nk	2yr	1 yr	1m	48,56	800	no	12/27/2011	mother	no	csa,mmf	no	0.8	no	no	nil	no		
9	2494/10	45	m	nk	2yr	18m	4m	22,26	nil	no	5/4/2011	spouse	no	csa,mmf	no	0.9	no	no	2m	11m	5m candida	
10	2508/04	44	m	nk	9y	8y	7y	18,22	nil	no	2005,8/4/12	spouse	no	csa,mmf	no	1.1	no	no	4m	8m	3m candida	
11	4933/10	33	m	nk	1 yr	10m	6m	20,22	nil	no	1/10/2012	mother	no	csa,mmf	yes	1.2	1a d11	d11	2m	no		8m hzv
12	1789/11	32	m	nk	15m	12m	3m	26,28	<15	no	2/9/2012	sister	no	csa,mmf	yes	1.4	1a d 10	d 10	3m	5m		5m hzv
13	2397/10	29	m	nk	2 yr	18m	18m	58,60	214,540	6m	7/20/2012	deceased	no	csa,mmf	yes	1.3	no	no	nil	no		6m hzv
14	3334/11	33	f	cgn	7 m	2 m	1m	24,28	<15	no	5/8/2012	mother	no	csa,mmf	yes	1.9	no	no	3m	6m		
15	5563/11	21	f	nk	8m	6m	2m	38,26	nil	no	4/10/2012	mother	no	csa,mmf	no	0.9	no	no	nil	no		
16	1247/10	45	m	nk	2yr	15m	6m	28,30	nil	no	7/2/2012	deceased	yes	csa,mmf	yes	-	1a d9	d10	2m	no	4m cmv	
17	5334/11	22	f	nk	2yr	20m	4m	24,32	nil	no	3/30/2012	mother	no	csa,mmf	yes	2.7	no	no	5m	no	5mcmv	
18	5086/11	40	m	nk	18m	15m	4m	48,50	4307	no	7/10/2012	spouse	no	csa,mmf	yes	3.2	no	no	nil	no		
19	1105/12	34	f	nk	7m	6m	1m	22,26	nil	no	12/18/2012	mother	no	csa,mmf	no	0.8	1a 1m	1m	3m	no	3m candida,cmv	
20	2231/12	21	f	nk	4m	3m	1m	21,24	nil	no	7/21/2012	mother	no	csa,mmf	no	0.8	1a 3m	5m	nil	no	5m candida	
21	5021/10	34	m	nk	8 y	6y	15m	22,24	nil	no	10/9/2013	deceased	yes	csa,mmf	no	1.2	no	no	4m	no	4m cmv	
22	1819/11	55	m	nk	4 y	2y	18m	18,22	nil	no	10/9/2013	deceased	yes	csa,mmf	no	1.2	no	no	nil	no	4m cmv	
23	2930/10	16	F	CGN	6 m	6m	2 m	36,27	nil	no	12/31/2010	g mother	no	csa,mmf	yes	1.3	no	no	nil	9m		
24	305/08	37	f	nk	5m	4m	2m	32,30	nil	no	4/21/2010	deceased	no	tac,mmf	yes	0.9	1a d7	d8	1m	no	3m candida	
25	3534/09	47	m	nk	10m	8m	2m	24,26	nil	no	7/6/2010	spouse	no	csa,mmf	no	0.9	no	no	2m	no	4m cmv	
26	2073/10	25	f	nk	8m	6m	2m	18,22	nil	no	12/14/2010	mother	no	csa,mmf	no	1	no	no	3m	no	5m cmv	
27	1342/10	34	m	cgn	11m	6m	3m	16,18	nil	no	11/18/2010	mother	no	csa,mmf	yes	1.3	1a d8	d9	2m	12m	4m cmv	
28	1671/11	28	m	nk	12m	7m	4m	14,16	nil	no	2/21/2011	mother	no	csa,mmf	no	1.2	no	no	nil	no		

S. No.	NC No.	SEPSIS		GRAFT BIOPSY							LIVER Bx	Latest ot,pt	LAST HCV RNA iu/l	post tx IFN.	latest s.cr.mg/dl	latest u.prot.	Outcomes			Dial. Dep	Follow Up
		URINE+ C/S	BLD.+ C/S	ATN/ATI	ACR	CNI TOX.	IFTA	TMA	Tx GLOM.	Others							Alive	Expiredcd	Nephrect		
1	3657/10	2m,6m	15m	d 12		9m	9m				not done	22,18	n d	no	2.7	nil	yes			no	34 m
2	4359/10		6m				8m				not done	48,52	66,748	no	1.6	nil	yes			no	31m
3	5747/10	4m					9m			fsgs	not done	24,28	n d	no	2.5	2 +	yes			no	33m
4	876/11		9m	1m,5m		5m			16m		not done	26,28	n d	no	3.2	nil	yes			yes	27m
5	3032/09	3m									not done	22,24	n d	no	1.2	nil	yes			no	26m
6	1747/11	4m		3m	2a 16d	6m					not done	56,62	833694	no	2	nil	yes			no	25m
7	1706/10										not done	50,54	46668	no	1.2	nil	yes			no	23m
8	1260/11										not done	20,22	n d	no	1.2	nil	yes			no	25m
9	2494/10	1m,4m	2m,5m				11m				not done	24,28	n d	no	2.2	nil	yes			no	21m
10	2508/04						8m				not done	20,22	n d	no	2.2	nil	yes			no	8m
11	4933/10				1a d11	8m					not done	28,30	n d	no	1.4	nil	yes			no	13m
12	1789/11		6m		1a d10		5m				not done	24,26	n d	no	2.4	nil	yes			no	12m
13	2397/10			d21		d 9					not done	24,28	n d	no	0.9	nil	yes			no	19m
14	3334/11	4m		d 7		6m	6m				not done	21,24	n d	no	1.7	nil	yes			no	21m
15	5563/11	3m									not done	20,24	nd	no	1.2	nil	yes			no	22m
16	1247/10	d12,	d14,17		1a d9	d9					not done	-	-				no	32 d		no	-
17	5334/11		4m	d 10							not done	56,68	234,657	yes	3.2	nil	yes		12 d	yes	24m
18	5086/11		4m	d 12							not done	22,26	n d	no	3.8	nil	yes		16d	yes	19m
19	1105/12				1a 1m						not done	20,24	n d	no	1.2	nil	yes			no	14 m
20	2231/12		5m		1a 5m			7m			not done	18,22	n d	no	1.3	nil	yes			no	17m
21	5021/10										not done	20,24	n d	no	1.2	nil	yes			no	5m
22	1819/11										not done	22,26	n d	no	1.1	nil	yes			no	5m
23	2930/10						9m, 30%				not done	18,20	n d	no	2	nil	yes			no	37 m
24	305/08				1a d 7						not done	16,20	n d	no	0.8	nil	yes			no	46 m
25	3534/09		5m,7m								chr.hepat.	48,52	n d	no	1.2	nil	yes			no	31 m
26	2073/10	4m	6m,9m								not done	20,24	n d	no	1	nil	yes			no	36m
27	1342/10	3m	6m,10m		1a d8		12m,30%				not done	18,22	n d	no	2.4	nil	yes			no	35m
28	1671/11																				

GLOSSARY

CMV	-	Cytomegalovirus
UTI	-	Urinary Tract Infection
HBV	-	Hepatitis B virus
HCV	-	Hepatitis C virus
PCR	-	Polymerase Chain Reaction
TAC	-	Tacrolimus
MMF	-	Mycophenolate Mofetil
PDN	-	Prednisolone
AZA	-	Azathioprine
CYC	-	Cyclosporine
CNI	-	Calcineurin Inhibitor
GDF	-	Graft Dysfunction
DGF	-	Delayed Graft Function
ATN	-	Acute Tubular Necrosis
NODAT	-	New Onset of Diabetes Mellitus
ART	-	Antirejection therapy
IFN	-	Interferon
ACR	-	Acute Cellular Rejection

KEY TO MASTER CHART

A.C.R.	-	Acute Cellular Rejection
Bx	-	Biopsy
C/S	-	Culture And Sensitivity
CGN	-	Chronic Glomerulonephritis
Cyclo/MMF	-	Cyclosporine/Mycophenoloate Mofeti;
D/W S.Cr.,CREAT	-	Discharge with S. Creatitine
Dial.Dependency	-	Dialysis Dependency
DOT	-	Date of Transplant
Du, Dur,	-	Duration
F	-	Female
F.U	-	Follow Up Duration
FUN	-	Fungal
GDF	-	Graft Dysfunction
H.Z	-	Herpes Zoster
HCV	-	hepatitis C virus
HES	-	Herpes Simplex
Immunosupp.	-	Immunosuppressants
M	-	Month
M	-	Male
Nephrect.	-	Nephrectomy
NKD	-	Native Kidney Disease Not Known
NO.	-	Number
OT	-	SGOT (Serum Glutamic Oxaloacetic Transminase)
PT	-	SGPT (Serum Glutamic Pyruvic Transaminase)
RNA	-	Ribonucleic Acid
TMA	-	Thrombotic Microangiopathy
TOX.	-	Toxicity
Y ,Yr.	-	Year